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Influence of thyroid status on electrolyte profile in dogs with chronic kidney disease

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Abstract
The present study was conducted to evaluate the influence of thyroid status on electrolyte profile in dogs with chronic kidney disease. A total of 72 client-owned dogs aged between two to ten years, presented to the Veterinary College Hospital, Bangalore were included in this study. The clinically healthy dogs were assigned to Group I. Euthyroid dogs with chronic kidney disease were in Group II and hypothyroid dogs with chronic kidney disease were assigned to Group III. The selected dogs were in the age ranges of 2-4, >4-6, >6-8 and >8-10 years comprising of six dogs in each age range. The dogs of various breeds and of either sex were included. Serum samples obtained were utilised for assay of serum electrolytes such as Na^+, K^+, Cl^-, Ca^{2+} and P_i. Group II had significantly higher P_i, K^+ and significantly lower Na^+ compared to Group I (control) at all age ranges. Group III had significantly higher P_i, K^+ and significantly lower Ca^{2+} and Na^+ compared to Group I at all age ranges. The Group III had significantly lower Ca^{2+} and significantly higher P_i compared to Group II at all age ranges. When the age ranges were compared, significantly higher P_i was noted in Group III at >8-10 years compared to 2-4 years and significantly higher serum K^+ was noted at >8-10 years when compared to 2-4 years age range in all the groups of study indicating age related changes in the functioning of kidneys and thyroid gland. In the present study, it is concluded that renal dysfunction had marked influence on serum electrolyte profile, while, hypothyroidism had additive effect on renal functional parameters mainly indicating the exaggeration of renal dysfunction.

Keywords: Dogs, chronic kidney disease, hypothyroidism, electrolytes

Introduction

Maintenance of homeostasis of metabolic functions in all body organs is critical in all living beings. This balance is achieved by actions of hormones, enzymes, minerals, vitamins, electrolytes and various metabolites along with body fluids. Chronic kidney disease (CKD) occurs when the compensatory mechanisms of chronically diseased kidneys are no longer able to maintain adequate functions to regulate electrolyte, water, and acid-base homeostasis. CKD is the third most common cause of death in dogs (Chew *et al.,* 2011) [1]. Brown (2007) [2] estimated the incidence of CKD in the general population of dogs as 0.5–1.5%. Further, O'Neill *et al.* (2013) [3] reported that the prevalence of CKD increased to 15% in dogs over 10 years of age.

Hypothyroidism in dogs may result from dysfunction of any part of the hypothalamic-pituitary-thyroid axis and may be acquired (most common) or congenital. The prevalence of canine hypothyroidism was from 0.2 % to 0.8 %, the mean age at diagnosis was 7 years, with a range of 0.5 to 15 years and there was no association with breed, gender, or neuter status (Scott-Moncrieff, 2007) [4]. The effects of thyroid dysfunction on the kidney included changes in renal blood flow, glomerular filtration rate (GFR), tubular secretory and absorptive capacity, electrolyte pumps and kidney structure. Further, derangement in kidney function is associated with abnormalities in thethyroid hormone physiology. The effects of impaired kidney function may lead tohypothyroidism, hyperthyroidism and non-thyroidal illness which are associated withderanged cardiovascular function which will adversely affect the prognosis of CKD.

Extensive perusal of literature revealed that clinical studies pertaining to comorbid conditions involving hypothyroidism and chronic kidney disease are meager or not available in the studies on dogs. Therefore, the present study was conducted in dogs with a view to evaluate influence of thyroid status on electrolyte profile in dogs with chronic kidney disease.

Materials and Methods

A total of 72 client-owned dogs aged between two to ten years, presented to the Veterinary College Hospital, Bangalore, were included in this study. The initial screening of the dogs was done based on the case history reports and classical clinical signs suggestive of chronic kidney disease and those of hypothyroidism were considered. Later, the dogs were subjected to diagnostic studies which included thyroid profile, renal biomarkers and serum biochemistry profiles for final inclusion of dogs into the particular study groups. The euthyroid dogs having without any renal disorders (clinically healthy) were taken as control group (Group I). Euthyroid dogs that suffered from CKD were considered as Group II. Hypothyroid dogs that suffered from CKD were considered as Group III. The selected dogs were in the age group of 2-4 years, >4-6 years, >6-8 years and >8-10 years that comprised of six dogs in each age group belonging to various breeds of either sex were included in the present study. A single blood sample from the dogs suspected for CKD and hypothyroidism and as well as from clinically healthy dogs were collected at the time of presentation to clinics. Serum was separated and stored at - 20 ℃ until further assay.

Analysis of serum samples

Serum calcium was estimated by Arsenazo III method as suggested by Bagainski (1973) [5] and Faulkner and Meites (1982) [6], serum inorganic phosphorus was estimated by UV method as suggested by Fiske and Subbarow (1925) [7] and Daly and Ertingshausen (1972) [8], serum sodium was estimated by a colorimetric method as suggested by Trinder (1951) [9] and Maruna (1958) [10], serum potassium was estimated by turbidity method as suggested by Terri and Sesin (1958)[11] and Sunderman and Sunderman (1959) [12] and serum chloride was estimated by a colorimetric method as suggested by Schoenfeld and Lewellen (1964) [13] and Skeggs and Hochstrasser (1964) [14] using the commercially available kits manufactured and supplied by M/s. Swemed Diagnostics, Bangalore-560062.

Statistical Analysis

The data obtained were analysed statistically by two way ANOVA with the application of Bonferroni post-test using 'Graph Pad Prism' version 5.01 (2007) computerized software. The values were expressed as Mean ± Standard Error and the level of significance or non-significance was determined at P value of 0.05.

Results and Discussion
Serum Calcium

Table 1: Mean ± SE values of serum Calcium (mmol/L) in different groups of dogs (n=6).

Group	2-4 years	>4-6 years	>6-8 years	>8-10 years
Group I	2.63 ± 0.05[b]	2.56 ± 0.12[b]	2.77 ± 0.06[b]	2.83 ± 0.08[b]
Group II	2.50 ± 0.07[b]	2.41 ± 0.08[b]	2.63 ± 0.06[b]	2.61 ± 0.07[b]
Group III	2.12 ± 0.04[a]	2.06 ± 0.07[a]	2.13 ± 0.07[a]	2.17 ± 0.05[a]

The values with different superscripts (a, b, c) within a column differ significantly (P<0.05).

In the present study, serum calcium levels in Group III were significantly lower at all stages of age compared to Group I and Group II (Table 1) indicating the primary influence of hypothyroidism in decline of serum calcium levels.

In the aspect of hypothyroidism, these observations are in concurrence with the reports of Yousif et al. (2012) [15] in dog studies and similarly Schmitz et al. (2001) [16] in humans. The results in Group III are attributed to the effects of thyroid hormone on regulation of blood calcium levels by releasing calcium from the cells wherein, less thyroxine enters the cells in hypothyroid subjects due to lower levels of thyroid hormones and less calcium is released. Apart from this, in hypothyroidism there is an impaired ability to mobilize calcium from bone as the osteoclasts are less responsive to the effects of parathyroid hormone than normal, as a consequence parathyroid hormone secretion may further be increased. At the level of kidneys, low levels of thyroid hormones are accompanied by decreased c-AMP levels in the brush border cell of renal tubules leading to decreased calcium reabsorption from tubules (Kumar and Prasad, 2002) [17]. It was also reported that low thyroid levels decrease intestinal brush border absorption of calcium from diet resources (Kumar and Prasad, 2003) [18].

Significant decrease in calcium with significant increase in phosphorus may also be attributed to impairment of calcitonin production from thyroid hormone (Cunningham, 2002) [19], and metabolic derangements induced by thyroid hormone deficiency, such as altered calcium homeostasis (Rossmeisl, 2010) [20].

In chronic kidney disease, the disturbances of serum calcium concentration may occur in renal failure for several reasons. An acute decrease in GFR may lead to an abrupt increase in serum phosphorus concentration, causing a decrease in serum calcium concentration by the law of mass action. The decrease in serum ionized calcium concentration stimulates parathyroid hormone synthesis and release, which act to increase the calcium concentration back to normal. On the other hand, chronic renal failure may cause parathyroid hyperplasia which rarely leads to hypercalcemia (Langston, 2008) [21]. Hyperparathyroidism was present in 100 % of dogs with moderate or severe CKD, while calcitriol was significantly lower compared with a control group, but still in the reference range in most dogs(Gerber et al., 2003) [22]. Disturbances in calcium and vitamin D metabolism that arise owing to CKD diminish the level of activation of the calcium-sensing receptor (CaSR) leading to increases in PTH secretion, PTH synthesis, and parathyroid gland hyperplasia (Goodman and Quarles, 2008) [23]. Metabolic acidosis increased the ionized calcium fraction, but more than 50 % of dogs with CKD and metabolic acidosis were hypocalcemic (Kogika et al., 2006) [24].

Serum Inorganic Phosphorus

Table 2: Mean ± SE values of serum inorganic phosphorus (mmol/L) in different groups of dogs (n=6).

Group	2-4 years	>4-6 years	>6-8 years	>8-10 years
Group I	1.53 ± 0.04[a]	1.54 ± 0.03[a]	1.53 ± 0.03[a]	1.50 ± 0.03[a]
Group II	1.84 ± 0.03[b]	1.87 ± 0.05[b]	1.77 ± 0.02[b]	1.82 ± 0.07[b]
Group III	2.06 ± 0.08[cx]	2.10 ± 0.09[cxy]	2.23 ± 0.05[cxy]	2.29 ± 0.09[cy]

The values with different superscripts (a, b, c) within a column differ significantly (P<0.05).
The values with different superscripts (x, y, z) within a row differ significantly (P<0.05).

In the present study, the serum inorganic phosphorus levels in Group II and Group III were significantly higher at all stages of age compared to Group I revealing the primary effect of

Chronic kidney disease in elevated levels of serum inorganic phosphorus in these dogs (Table. 2).

In chronic kidney disease in both Group II and Group III, these observations are in agreement with the studies of Polzin *et al.* (2005) [25], Girishkumar (2011) [26] and Oburai *et al.* (2015) [27] who also reported an increased serum phosphorus levels in dogs suffering from chronic kidney disease. Langston (2008) [23] opined that the dietary phosphorus is readily absorbed from the gastrointestinal tract and excreted by the kidneys, an acute decrease in GFR may lead to an abrupt increase in serum phosphorus concentration, causing a decrease in serum calcium concentration by the law of mass action. Decreased excretion commonly lead to hyperphosphatemia in patients with chronic renal failure. The pathogenesis of severe hyperphosphatemia in CKD dogs is explained in the aspect of involvement of parathyroid gland [25].

The serum inorganic phosphorus values in Group III were significantly higher compared to Group II and Group I. These observations in hypothyroid dogs were in agreement with Al-Tonsi *et al.* (2004) [28] and Yousif *et al.* (2012) [15] who also reported significantly elevated phosphate levels in hypothyroid patients. It is concluded that the effect on low thyroid hormone levels on reducing the GFR primarily leads to retention of phosphorus and apart from this the low calcium levels in hypothyroid subjects may stimulate calcitonin and PTH secretion further leading to the elevation of serum phosphate concentration.

The serum inorganic phosphorus values at >8-10 years were significantly higher compared 2-4 years in Group III indicating an age related alteration in functionality of thyroid and kidneys leading to impaired excretion of phosphate in urine as the age advanced.

Serum Sodium

Table 3: Mean ± SE values of serum sodium (mmol/L) in different groups of dogs (n=6).

Group	2-4 years	4-6 years	6-8 years	8-10 years
Group I	145.13 ± 0.30[b]	146.38 ± 0.37[b]	146.13 ± 1.75[b]	146.38 ± 0.49[b]
Group II	140.90 ± 1.13[a]	141.62 ± 0.97[a]	141.52 ± 0.86[a]	141.71 ± 1.24[a]
Group III	139.79 ± 1.15[a]	140.31 ± 1.19[a]	141.03 ± 1.42[a]	140.16 ± 1.51[a]

The values with different superscripts (a, b, c) within a column differ significantly (P<0.05).

In the present study, the serum sodium levels in Group II were significantly lower compared to Group I at various stages of age indicating the primary influence of chronic kidney disease in decline of serum sodium. (Table 3).These observations are in accordance with the reports of Pak (2000) [29] and Carlson and Bruss (2008) [30]. It is concluded that the increase in the sodium excretion by the remaining functional nephrons observed in CKD is due to a decrease in the tubular reabsorption of this electrolyte with increase in the excreted fraction of sodium in CRF by comparison with patients with intact renal function. Hyponatremia also is relatively common in patients with ESRD, and hypernatremia is rare. (Combs and Berl, 2014) [31].

Carlson and Bruss (2008) [30] reported that hyponatremia can occur when there is excessive renal sodium loss with intrinsic renal disease or it may be due to relative water excess leading to excessive circulating volume in nephrotic syndromes.

The serum sodium levels in Group III were significantly lower when compared to Group I at all stages of age. In the

aspect of hypothyroidism, these observations are in accordance to the findings of Zimmerman *et al.* (1988) [32], Iglesias and Díez (2009) [33] and Yousif *et al.* (2012) [15] in hypothyroid dogs. According to Schmitt *et al.* (2003) [34] hyponatremia due to impaired water excretion is a common complication of clinical hypothyroidism. They demonstrated reduced capacity to achieve maximal urinary dilution due to non-osmotic arginine vasopressin release, as well as impaired urinary concentrating ability, increased urinary sodium excretion, increased fractional excretion of sodium, and impaired tolerance of sodium restriction in the hypothyroid subjects. The molecular basis for hyponatremia in hypothyroidism is explained as; plasma renin activity and plasma aldosterone might be suppressed (Saruta *et al.*, 1980) [35], activity of Na/K ATPase and the tubular transport capacity is reduced (Garg *et al.,* 1985) [36], Na+-H exchanger activity is reduced in hypothyroidism (Marcos-Morales *et al.*, 1996) [37] and Na+-H+exchanger-3 and Na+-K+-ATPase were decreased in the hypothyroid rats (Cadnapaphornchai *et al.*, 2003) [38]. The significant decrease in sodium could be attributed to decrease in the renal blood flow and the glomerular filtration rate secondary to hypothyroidism that leads to decreased sodium reabsorption in the proximal tubules (Allon *et al.,* 1990) [39], impairment in the concentrating and diluting capacities of the distal tubules (Ajaykumar, *et al.,* 2013) [40], leading to increased excretion of sodium and finally resulting in decrease serum sodium level.

Serum Potassium (K+)

Table 4: Mean ± SE values of serum potassium (mmol/L) in different groups of dogs (n=6).

Group	2-4 years	>4-6 years	>6-8 years	>8-10 years
Group I	4.63 ± 0.03[ax]	4.68 ± 0.07[axy]	4.74 ± 0.06[axy]	4.85 ± 0.04[ay]
Group II	5.07 ± 0.05[bx]	5.11 ± 0.06[bxy]	5.13 ± 0.11[bxy]	5.30 ± 0.04[by]
Group III	5.14 ± 0.04[bx]	5.21 ± 0.06[bxy]	5.35 ± 0.08[bxy]	5.43 ± 0.07[by]

The values with different superscripts (a, b, c) within a column differ significantly (P<0.05).
The values with different superscripts (x, y, z) within a row differ significantly (P<0.05).

In the present study, the serum potassium levels of Group II and Group III were significantly higher when compared to Group I (Control) at all stages of age revealing the primary influence of chronic kidney disease in elevation of serum potassium levels (Table 4).

These observations in the present study revealed mild hyperkalemia in dogs suffering from CKD are in agreement with the findings of Adams (2004) [41], Girishkumar *et al.* (2011) [26],Chew and Gieg (2006) [42] and Chang *et al.* (2016) [43] in dog studies. Similar observations were noted by Mount (2011) [44] and Dhondup and Qian (2017) [45] who also reported hyperkalemia in human patients with CKD. According to Mount (2011) [44] in case of CKD the renal and extra-renal mechanisms facilitate the ability to excrete40-100 mEq of potassium per day even with GFR as low as 10 ml/min, and hence maintains normal levels of potassium. Below 10 ml/min GFR the ability to excretedaily load of potassium is insufficient to maintain normal levels. The presence of hyperkalemia in CKD dogs is primarily attributed to decreased excretory capacity of the kidneys as the potassium follows renal elimination, lowered renal function predisposes to hyperkalemia. Saruta *et al.* (1980) [35] reported suppression of plasma renin activity and plasma aldosterone in patients with hypothyroidism and this may be the reason

for exaggerated sodium excretion and decrease in potassium excretion.

In Group I, Group II and Group III, the serum potassium levels at >8-10 year age were significantly higher compared to 2-4 years age. These observations are in agreement with the reports of Lowseth *et al.* (1990) [46] and Chang *et al.* (2016) [43] in dogs. The rising potassium concentration with age was notable and likely to reflect the combined influence of age on absorption, excretion and transcellular shifts. As ageing is associated with decrease in estimated GFR (Shlipak *et al.,* 2009) [47] and a higher concentration of potassium is necessary to elicit an aldosterone response in elderly (Mulkerrin *et al.,* 1995) [48]. It is also concluded that, the delicate mechanisms maintaining potassium homeostasis in renal failure may be disrupted by several factors and lead to hyperkalemia. The gradient between intracellular and extracellular potassium is modified by acidosis, cationic amino acids, and sudden increases in plasma osmolality. Absence of aldosterone, resistance of renal tubules to mineralocorticoids, may jeopardize the adaptive increases in tubular potassium secretion. Finally, an increased endogenous or exogenous load of potassium may precipitate potassium intoxication.

Serum Chloride (Cl⁻)

Table 5. Mean ± SE values of serum chlorides (mmol/L) in different groups of dogs (n=6).

Group	2-4 years	>4-6 years	>6-8 years	>8-10 years
Group I	108.64 ± 2.27	108.03 ± 2.02	106.36 ± 2.48	104.57 ± 1.01
Group II	104.98 ± 2.03	103.09 ± 1.70	101.82 ± 1.62	101.27 ± 1.60
Group III	102.83 ± 1.34	102.94 ± 1.57	101.42 ± 1.94	100.09 ± 1.38

None of the values in a column or row differ significantly (P>0.05).

In the present study, the serum chloride levels did not depict any significant variations among Group I, Group II and Group III at various stages of age although numerically lower serum chloride levels were observed in Group II and Group III compare to Group I at different stages of age (Table. 5).

Zimmerman *et al.* (1988) [32] reported that, in hypothyroid dogs there is a reduced proximal tubular absorption of sodium, chloride, and water as well as the reduced expression of renal basolateral chloride channel. Thus, reduced chloride reabsorption which increased the distal chloride delivery, triggering the macula densa mediated tubulo-glomerular feedback which can reduces the RAAS activity leading to fall in the GFR.

The probable reason for no statistical differences noted in various groups of dogs might be due to metabolic acidosis secondary to reduction in GFR in CKD dogs. As metabolic acidosis is associated with loss of bicarbonate with retention of chloride by the kidneys (primary normal anion gap or hyperchloremic metabolic acidosis).So in such cases, one mechanism is losing chloride and the other mechanism is responsible for retaining the chloride by the kidneys.

Conclusion

It is hypothesized that hypothyroidism could affect the functions of kidney and vice versa. The findings of the study will have lot of clinical relevance since, a multifactorial approach in treating patients with diseases affecting either thyroid or kidney would prove vital to avoid missing subtle but clinically relevant abnormalities.

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